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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/623,205	PALASIS, MARIA	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-14,17,18,20,21,24-31,35 and 39-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-14,17,18,20,21,24-31,35 and 39-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/28/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 7-14, 17, 18, 20, 21, 24-31, 35, 39-45 as amended and new claims 46 and 47 (2/27/2007) are pending and under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 7-14, 17, 18, 20, 21, 24-31, 35, 39-45 as amended and new claim 46 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Kocher et al. ("Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomycete apoptosis, reduces remodeling and improves cardiac function". Nature Medicine. April 2001. Vol. 7, No. 4, pages 430-436) and Kalka et al. ("Transplantation of *ex vivo* expanded endothelial progenitor cells for therapeutic neovascularization". PNAS. March 28, 2000. Vol. 97, No. 7, pages 3422-3427) taken with US 5,199,942 (Gillis) (IDS reference).

Claims are directed to a method of producing a graft of muscle tissue in damaged or diseased tissue of a human in need thereof, comprising steps of (a) administering a mobilization factor to a donor to mobilize stem cells into peripheral blood, the donor being HLA-matched to a recipient; (b) isolating stem cells from peripheral blood of the donor by apheresis; and (b) implanting a population of the isolated stem cells into the tissue of recipient; whereby implantation produces a graft of muscle tissue in the damaged or diseased tissue. Some claims

are/are further drawn to the damaged or diseased tissue(s) including tissue striated muscle, ischemic tissue, necrotic tissue, myocardium, skeletal muscle, heart. Some claims are further drawn to administration of engraftment factor to promote engraftment of the stem cells in the subject. Some claims are further drawn to fractionating the stem cells prior implantation including FACS and density gradient centrifugation. Some claims are further drawn to additional step of ex vivo expanding the cells prior to the implanting step. Some claims are further drawn to implanting the cells at the site of disease or damage.

New claim 46 is further drawn to the use of hematopoietic stem cells in the method for of treating damaged muscle tissue.

The references by Kocher et al. and Kalka et al. are relied for the disclosure of a method of treating damaged or diseased tissue and/or of producing an improved and functional graft of muscle tissue in the damaged or diseased tissue of a mammalian subject by implanting peripheral blood derived stem cells. The cited references teach that transplantation of the donor peripheral blood derived stem cells results in neovascularization and amelioration of the damaged muscle tissues such as striated muscle, ischemic tissue, necrotic tissue, myocardium, skeletal muscle, heart. Both cited references demonstrate that the donor peripheral blood derived stem cells were incorporated or implanted into recipient damaged tissues, thus, producing an improved and functional graft of muscle tissue in the recipient. Both cited references recognize presence of stem cells in circulating blood or peripheral blood. The reference Kocher et al. also teaches mobilization of stem cells from bone marrow into peripheral blood by administration of mobilization factors to the stem cell donor. The reference Kalka et al. also teaches that *ex vivo* culture strategy allows expansion and considerable increase in the original number of harvested

cells (page 3426, col. 2, par. 2). Both cited references suggest that transplantation of stem and/or progenitor cell population has potential to significantly improve damaged or diseased tissue in patients, and, thus, humans. Both cited references suggest transplantation of stem cells alone in combination with currently used therapies or with cytokines. For example: see Kocher et al. at abstract and see Kalka et al. at last lines of the articles on page 3427.

The cited reference references by Kocher et al. and Kalka et al. disclose the use of hematopoietic stem cells including CD34+ in the methods for of treating damaged muscle tissue and/or improving cardiac function.

The cited references recognize and suggest combined therapies or transplantation of stem cells with additional drugs but they are lacking particular disclosure about some particular mobilization and engraftment factors. However, US 5,199,942 (Gillis) teaches administering engraftment factors including GM-CSF, IL-3, SCF and others following transplantation of hematopoietic cells in the method for improving cell transplantation (col. 3, lines 39-45). US 5,199,942 also teaches administering recruitment or mobilization factors including GM-CSF, IL-3, SCF and others prior to cell collection (col. 3, lines 30-36) and ex vivo expansion of progenitor cells (col. 3, lines 46-52) in the method for improving cell transplantation.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to administer various mobilization and/or engraftment factors in combination with stem and/or progenitor cell transplantation with a reasonable expectation of success for improving cell transplantation as suggested by Kocher et al. and Kalka et al. and as taught by US 5,199,942 (Gillis). One of skill in the art would have been motivated to *ex vivo* expand the stem or progenitor cells prior transplantation for the expected benefits in expanding

or increasing number of harvested cells as taught by Kalka et al. and taught by US 5,199,942 (Gillis). One of skill in the art would have been motivated to use cells derived from a donor that is HLA-matched to the recipient for the expected benefits in minimizing immune response and avoiding transplant rejection.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

2. Claims 1, 7-14, 17, 18, 20, 21, 24-31, 35, 39-45 as amended and new claim 47 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,387,369 (Pittenger et al) and US 6,261,549 (Fernandez et al) taken with Orlic et al. (IDS reference; Nature. 2001, Vol. 410, pages 701-705) and Orlic et al. ("Cytokine-mobilized stem cells traffic to infracted hearts and regenerate functional myocardium resulting in improved survival". Blood. 2001. Vol. 98, No. 11, part 1, page 810a.).

Claims are directed to a method of producing a graft of muscle tissue in damaged or diseased tissue of a human in need thereof, comprising steps of (a) administering a mobilization factor to a donor to mobilize stem cells into peripheral blood, the donor being HLA-matched to a recipient; (b) isolating stem cells from peripheral blood of the donor by apheresis; and (b) implanting a population of the isolated stem cells into the tissue of recipient; whereby implantation produces a graft of muscle tissue in the damaged or diseased tissue. Some claims are/are further drawn to the damaged or diseased tissue(s) including tissue striated muscle,

ischemic tissue, necrotic tissue, myocardium, skeletal muscle, heart. Some claims are further drawn to administration of engraftment factor to promote engraftment of the stem cells in the subject. Some claims are further drawn to fractionating the stem cells prior implantation including FACS and density gradient centrifugation. Some claims are further drawn to additional step of ex vivo expanding the cells prior to the implanting step. Some claims are further drawn to implanting the cells at the site of disease or damage.

New claim 47 is further drawn to the use of mesenchymal stem cells in the method for of treating damaged muscle tissue.

US 6,387,369 teaches a method for regeneration of repair of striated cardiac muscle or for producing a graft of muscle tissue by implanting mesenchymal stem cells (MSCs) in the damaged tissue, for example: see entire document including col. 1, lines 41-50. The preferred stem cells are autologous MSC cells (col. 2, line 23), thus, clearly being HLA-matched cells.

The source for the isolation of the MSCs in the method of administration is a generic "MSC-containing tissue" as disclosed by US 6,387,369, for example: col. 1, line 61. However, US 6,261,549 teaches that the MSCs intended for administration and muscle tissue repair are collected from the peripheral blood of the donors treated the growth factors G-CSF and/or GM-CSF, for example: see entire document including abstract. The cited patents US 6,387,369 and US 6,261,549 also encompass cell sorting and ex-vivo expansion of the cells prior to administration.

Further, the cited references by Orlic et al. teach and demonstrate that bone marrow-derived stem cells mobilized by cytokines into peripheral blood regenerate infarcted myocardium.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use mesenchymal stem cells mobilized into peripheral blood for implantation into the damaged striated muscle tissue with a reasonable expectation of success in producing a graft of muscle tissue because the prior art teaches and/or suggests the use of mesenchymal stem cells mobilized by cytokines into peripheral blood for regeneration of striated cardiac muscle as adequately demonstrated by the cited references. The prior art clearly teaches the use of autologous MSC cells, inherently being HLA-matched cells, as preferred source of cell for transplantation. In alternative, one of skill in the art would have been motivated to use cells derived from a donor that is HLA-matched to the recipient for the expected benefits in minimizing immune response and avoiding transplant rejection. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 2/27/2007 have been fully considered but they are not found persuasive.

1. With regard to the claim rejection under 35 U.S.C. 103(a) as being unpatentable over Kocher et al. and Kalka et al. taken with US 5,199,942 (Gillis) applicant argues that the cited references are silent about the use of HLA-matched donor and that the methods Kocher et al. and Kalka et al. do not demonstrate production of "muscle cells" (response pages 10-11).

Although the particular experimental models in the methods Kocher et al. and Kalka et al involve implantation of human stem cells into rodent models, one of skill in the art would clearly be motivated to use stem cells from human HLA matched donor for human implantation for the expected benefits in avoiding immune reaction, graft rejection and GVHD complications.

With regard to argument as drawn to development or exclusive production of "muscle cells", it is noted that the claimed term "a graft comprising muscle cells in the damaged or diseased tissue" is rather vague and broad as claimed and as disclosed. No histological analysis of a newly formed "graft comprising muscle cells" from the implanted stem cells including hematopoietic cells is demonstrated by the applicant (specification pages 24-26). Thus, given a broadest reasonable interpretation to the claimed invention, a generic "graft comprising muscle cells" as a whole muscle tissue also comprises some vascular structures. The revascularization protects muscle cells against apoptosis and provides for regeneration and improvement of muscle tissue function as a whole. The cited reference by Kalka et al. teaches that transplantation of human peripheral blood derived stem cells or endothelial progenitors resulted in improved recovery and capillary density in the skeletal muscle tissue of the ischemic hindlimbs (page 3425, last par.), thereby, providing for the muscle tissue salvage (page 3426, col. 1). Thus, the cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims. Moreover, endothelial progenitor cells are inherent progenitors of heart muscle cells in view of the newly cited IDS reference by Strauer et al. (page 930, col.1, last par.).

2. With regard to the claim rejection under 35 U.S.C. 103(a) as being unpatentable over US 6,387,369 (Pittenger et al) and US 6,261,549 (Fernandez et al) taken with Orlic et al. (Nature. 2001, Vol. 410, pages 701-705) and Orlic et al. (Blood. 2001. Vol. 98, No. 11, part 1, page 810a) applicant's main argument is that the cited references are silent about HLA-status of donor of stem cells. However, the stem cells that are used for muscle repair in the method of US 6,387,369 (Pittenger et al) are mesenchymal stem cells. It is well known that mesenchymal stem cells are immunologically neutral cells, they are invisible for immune system and they do not express immunologically relevant cell surface markers. Therefore, MSCs need not to be MHC (or HLA) matched as evidenced by US 6,355,239, for example: see col. 1, lines 20-50. Thus, the prior art references cited in the office action are silent about HLA status of donor stem cells since the use of mesenchymal stem cells does need matching of donors accordingly HLA status.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

May 9, 2007

V. Afremova

VERA AFREMOVA

PRIMARY EXAMINER